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PHARMACOLOGICAL PROPERTIES OF THE PRODUCTS OF THE REACTION OF EPITHIOCHLORHYDRIN WITH BENZIMIDAZOLES

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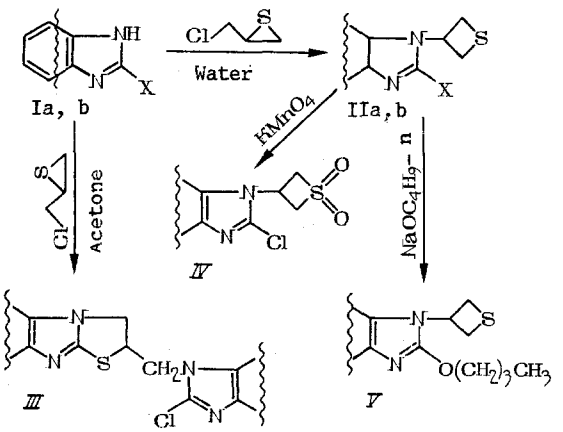
UDC 615.276:547.785.5

1,2-Disubstituted and condensed benzimidazoles display a variety of biological activities [1, 2]. Oxiranes are widely used for the synthesis of biologically active benzimidazole derivatives [4, 7]. There are no literature data on the use of thiiranes for this purpose. Some chemical and pharmacological properties of the alkylation products of 2-substituted benzimidazoles (Ia, b) with epithiochlorhydrin have been studied in the present work.



X=Cl(Ia,IIa), SO_2CH_3(Ib,IIb)

It was established that the structure of the alkylation product was determined by the solvent used. We have reported [6] that a thiirane–thietane rearrangement occurs on heating 2-substituted benzimidazoles (Ia, b) with epithiochlorhydrin in aqueous medium in the presence of potassium hydroxide and that 2-substituted 1-(3-thietanyl)-benzimidazoles (IIa, b) are formed. However boiling compound (Ia) with epithiochlorhydrin in acetone in the presence of potassium carbonate leads in high yield to the dihydrothiazolo[3,2-a]benzimidazole (III), in agreement with the data of [5].

On reacting the 1,2-disubstituted benzimidazole (IIa) with a solution of potassium permanganate in acetic acid, oxidation of the sulfur atom of the thietane ring occurs with

Bashkir Medical Institute, Ufaz. Perm Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 27, No. 3, pp. 25-26, March, 1993. Original article submitted March 12, 1992.

 0091-150X/93/2703-0192$12.50

the formation of 2-chloro-1-[3-(1,1-dioxothietanyl)]benzimidazole (IV). The reaction of compound (IIa) with sodium n-butylate leads to the formation of 2-(n-butyloxy)-1-(3-thietanyl)-benzimidazole (V), i.e., replacement of the chlorine atom by an n-butyloxy group occurs but the thietane ring is not opened.

The structure of the new compounds was confirmed by data of elemental analysis, IR, PMR, and mass spectra. The PMR spectrum of dihydrothiazolo[3,2-a]benzimidazole (III) contains a multiplet at 4.30-5.20 ppm for 5H belonging to the protons of the dihydrothiazole ring and the exocyclic methylene group in addition to the signals for aromatic protons. The PMR spectrum of the 1,2-disubstituted benzimidazole (V) contained multiplets at 5.40-5.80 (NCH), 3.70-4.00 [$S(CH)_2$] and 3.04-3.34 ppm [$S(CH)_2$] characteristic of the thietane ring [6] in addition to signals for protons of the aromatic nucleus and the n-butyloxy group. Oxidation of the sulfur atom was confirmed by the presence in the IR spectrum of the benzimidazole (IV) of absorption bands at 1140 and 1320 cm^{-1} characteristic of sulfones [3]. The mass spectrum of compound (IV) contains the molecular ion ($M^{+\cdot}$) as two peaks of m/e 256 and 258 in a 3:1 ratio which indicates the presence of a chlorine atom and intense peaks for fragmentation ions of m/e 178 and 180 $[M-CH_2SO_2]^{+\cdot}$, 152 and 154 $[M-C_3H_5SO_2]^{+\cdot}$, and 143 $[M-CH_2-SO_2-Cl]^{+}$, which confirm the structure proposed.

EXPERIMENTAL (CHEMICAL)

The IR spectra were taken on a Beckman 620MX instrument as nujol suspensions. The PMR spectra were recorded on a Tesla BS-567 spectrometer (100 MHz), internal standard was TMS, solvent was trifluoroacetic acid. The mass spectra were obtained on a Kratos MS-80 instrument with the energy of the ionizing electrons 70 eV. TLC was carried out on Silufol UV-254 plates in n-butanol–acetic acid–water (4:1:2), visualized with iodine vapor. The elemental analysis data for C, H, Cl, N, and S of the compounds synthesized agreed satisfactorily with the calculated values.

The 1,2-disubstituted benzimidazoles (IIa,b) were synthesized as described in [6].

2-[1-(2-Chlorobenzimidazolyl)]methyl-2,3-dihydrothiazolo[3,2-a]benzimidazole (III). A mixture of benzimidazole (Ia) (2.25 g: 10 mmole), anhydrous potassium carbonate (1.38 g: 10 mmole), and epithiochlorhydrin (1.09 g: 10 mole) in acetone (100 ml) was boiled for 3 h. The mixture was cooled to 5-10°C, the solid filtered off, washed with water, and dried. Compound (III) (1.36 g: 80%) was obtained having mp 195-197°C (from ethanol) and R_f 0.73. PMR spectrum, δ, ppm: 4.30-5.20 (5H, m, NCH_2, SCH, and 2-CH_2N); 6.80-7.60 (8H, m, CH-ar.).

2-Chloro-1-[3-(1,1-dioxythietanyl)]benzimidazole (IV). A 7% solution of potassium permanganate (100 ml) was added in portions during 30 min to a solution of compound (IIa) (3.37 g: 15 mmole) in glacial acid (30 ml) at a temperature not exceeding 30°C. The solution was stirred at this temperature for 2 h, ice (100 g) was added, and stirring continued for 1 h further. The reaction mixture was decolorized with a saturated solution of sodium thiosulfate. The precipitated solid was filtered off, washed with water, and dried. Compound (IV) (3.52 g: 91%) was obtained having mp 187-188°C (from n-butanol). IR spectrum, cm^{-1}: 1140 and 1320 (SO_2), 730-770 (CH ar.). Mass spectrum, m/e (relative intensity, %): 258(12), 156(35), 180(52), 179(18), 178(100), 177(17), 154(8), 152(22), 143(32), 142(22), 129(18), 116(15), 115(14), 103(12), 102(43), 91(15), 90(58), 89(20), 77(22), 76(25), 75(29), 74(11), 73(12), 65(13), 64(55), 63(48), 62(30), 61(12), 57(14), 55(22), 52(18), 51(38), 50(39).

2-(n-Butyloxy)-1-(3-thietanyl)benzimidazole (V). Compound (IIa) (2.25 g: 10 mmole) was added to a solution of metallic sodium (0.28 g: 12 mmole) in n-butanol (50 ml) and the mixture boiled for 4 h. The mixture was cooled to 5-10°C, filtered, and the filtrate evaporated. The oily product was triturated with water. Compound (V) (1.99 g: 76%) was obtained having mp 57-60°C (from ethanol:water, 2:1) and R_f 0.86. PMR spectrum, δ, ppm: 0.66 (3H, t, J = 7 Hz, CCH_3); 0.94-1.84 [4H, m, $(CH_2)_2$]; 3.04-3.34 [2H, m, $(CH)_2$]; 3.70-4.00 [2H, m, $S(CH)_2$]; 4.42 (2H, t, J = 6 Hz, OCH_2); 5.40-5.80 (1H, m, NCH); 7.04-7.82 (4H, m, 4 CH ar.).

EXPERIMENTAL (PHARMACOLOGICAL)

White mice were used in experiments to study the overall action, toxicity, effect on central coordination mechanisms (rotating horizontal rod test), on mechanical tail irritation (tail clamping test) after intraperitoneal injection of the compounds synthesized. The

TABLE 1. Antiinflammatory Action of Compounds (II)-(V)

Compound	Increase of paw edema, %	
	after 3 h	after 5 h
IIa	20,6*	38,8*
IIb	22,1*	41,2*
III	31,0*	53,7
IV	18,8*	32,1*
V	47,3*	67,1
Control	64,4	80,1

*$p < 0.05$.

ability of compounds to inhibit agar inflammation was studied in experiments on white rats after intraperitoneal injection. Experiments were carried out by the generally accepted procedures.

The toxicity of the 1,2-disubstituted benzimidazoles (IIa, b), (IV), and (V) was more than 800 mg/kg. At the maximum dose (800 mg/kg) compounds (IIa, b), (IV), and (V) caused slight retardation and a reduction of motor activity. There was no analgesia (tail clamping test) or myorelaxation (rotating rod test). The LD_{50} of the dihydrothiazolobenzimidazole (III) was 560 mg/kg. At toxic doses compound (III) caused clonic convulsions in the first 5 min resulting in death of the animals.

All the synthesized compounds (II)-(V) on intraperitoneal injection at 50 mg/kg showed a marked inflammatory action 3 h after and compounds (IIa, b) and (IV) 5 h after the agar injection. The experimental results are given in Table 1, from which it is seen that the greatest antiinflammatory action was shown by the 1,2-disubstituted benzimidazole (IV) containing at position 1 a thietane ring having sulfur oxidized to sulfone.

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